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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/678,816	PARRY ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-96* is/are pending in the application.

4a) Of the above claim(s) *1-47,57,66 and 70-85* is/are withdrawn from consideration.

5)☒ Claim(s) *62 and 63* is/are allowed.

6)☒ Claim(s) *48-56, 58-61, 64, 65, 67-69 and 86-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-96 are all the pending claims for this application.

2. Claims 48, 60, 61, 67, 87 and 96 are amended in the Response of 7/27/07.

3. Claims 1-47, 57, 66 and 70-85 are withdrawn from examination.

4. Claims 48-56, 58-65, 67-69 and 86-96 are all the claims under examination.

5. Applicants amendments to the claims have necessitated new grounds for rejection.

Withdrawal of Rejections

Claims - 35 USC § 112, second paragraph

6. The rejection of Claims 48-56, 58-61, 64, 65, 67-69 and 86-96 for the recitation "derivative thereof" is withdrawn in view of the amendment of Claim 48 to delete the limitation.

Note- Applicants have addressed the rejection on p. 15 of the Response of 7/27/07 under 35 USC § 112, first paragraph for written description. Applicants are requested to review the Office Action of 3/27/07 for verification that Claims 48-56, 58-61, 64, 65, 67-69 and 86-96 were originally rejected under 35 USC § 112, second paragraph.

7. The rejection of Claim 87 for the recitation "is a polyclonal antibody" is withdrawn in view of the deleted limitation from the claim. Applicants' comments on the top of p. 11 of the Response of 7/23/07 are noted.

Claims - 35 U.S.C. § 112, first paragraph

Biological Deposit

8. The rejection Claims 62 and 63 because Applicant's specification does not make any assurances that restrictions imposed on each of the deposits will be irrevocably removed upon the granting of a patent (see "Condition of Deposit" MPEP 2410.01) is withdrawn. Applicants' statement of assurances on p. 13, ¶5 (lines 14-15) of the Response of 7/27/07 are acknowledged and of record.

9. The Examiner's position that the hybridoma, 14C7, would obtain benefit of the priority filing date (10/4/03) and the hybridoma, 94A7, would obtain benefit of the instant filing date (10/2/03) is maintained.

Applicants comments on p. 13 of the Response of 7/23/07 that "the PTO's position is contradictory to the case law holding that enablement is determined at the time of issuing of the patent, and these deposits made after filing are acceptable" are not understood. The priority determination is based on when in the application file history each of the hybridomas was found to meet the requirements under 112, 1st paragraph for written support (contemplation) and enablement.

Applicants are invited and encouraged to review U.S. Provisional Application No. 60/416,038 for any mention of the 94A7 hybridoma.

Enablement

10. The rejection of Claims 65 and 67-69 in lacking enablement for using the pharmaceutical application in any method or for just any application is withdrawn in view of Applicants' allegations on pp. 15-18 of the Response of 7/23/07.

In summary, Applicants allege "The term pharmaceutical is not to be construed as limiting the use in the treatment of diseases, for example, diagnostic uses are possible"; the anti-hepsin molecule is capable of binding to hepsin and useful for detection and targeting of tumor cells"; and the specification discloses enabling uses of antibody molecules, not only for detection of hepsin, but also for neutralization of hepsin molecules and/or activity thereof, and found to overcome the rejection of the pharmaceutical composition claims.

Applicants pharmaceutical composition claims are enabled for diagnosing or detecting cells expressing the modified hepsin molecule of SEQ ID NO:9 using the antibody or the antibody fragment which binds to the protein of SEQ ID NO:9.

Note- The Examiner specifically disagrees with Applicants assertion on p. 18, ¶2, lines 4-8 that an FDA standard applying the use of clinical trials has been required of them in order to meet the enablement requirement for the claims. Applicants are requested to identify in the Office Action of 3/27/07 by specific page, paragraph and line where the plain language for any such requirement is stated or implied.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. The rejection of Claims 61, 64, 65, 67-69 and 86-96 because Claim 61 is drawn to "A hybridoma which produces... the antibody fragment of claim 48" is maintained.

The amendment of Claim 61 to recite "or the antibody fragment of claim 48" and Applicants' allegations on p. 14 of the Response of 7/23/07 have been considered but are not found persuasive. The enclosed Wikipedia definition of "monoclonal antibodies" that Applicants rely upon for their arguments describes hybridomas *producing* only full length antibodies and not fragments of antibodies. The Examiner understands that generating antibody fragments from secreted monoclonal antibodies was well within the skill of the ordinary artisan at the time of the invention.

The specification at p. 46, lines 5-21 discloses that the clones deposited with the ATCC as PTA-4561 and PTA-5553 are the hybridoma cell lines 14C7 and 94A7, which produce the monoclonal antibody 14C7 and 94A7, respectively. The art teaches that a hybridoma is produced by the fusion between a B cell and a myeloma cell, which is a cancer cell that provides the resultant B cell-myeloma hybrid, or hybridoma, with the capacity to proliferate indefinitely and to secrete the full length monoclonal antibody having a single idiotype (see Campbell et al, Biology, 5th ed. pg. 856, 1999). Thus, when read in light of the specification and in view of the knowledge in the art, one of

ordinary skill in the art would not be reasonably apprised of the metes and bounds of "the antibody fragment of Claim 48" as presently claimed because a hybridoma secretes or produces full length mouse antibodies. Further, it is unclear if the claims are directed towards the hybridoma deposited with the ATCC as PTA-4621 or is some clone that is genetically engineered such that other forms of monoclonal antibodies are produced by other hybridomas. It is unclear what is contemplated by the phrase "the antibody fragment of Claim 48" and one of skill in the art could not determine the metes and bounds of the claimed invention as written.

New Grounds for Rejection

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

12. Claims 48-56, 64-69 and 86-93 are rejected under 35 U.S.C. 101 because the claimed invention, an antibody, is directed to non-statutory subject matter.

The claims read on an antibody that is found in nature. Products of nature do not constitute patentable subject matter as defined in 35 USC 101. See MPEP 2105. Since an antibody does not exist in nature in purified form, it is suggested that Applicant use the language "isolated" or "purified" in connection with the antibody to identify a product that is found in nature.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

13. Claims 61, 64, 65, 67-69 and 86-96 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a WRITTEN DESCRIPTION rejection.

Claims 61, 64, 65, 67-69 and 86-96 are drawn to a hybridoma *producing* an antibody fragment which binds to a modified hepsin molecule consisting of SEQ ID NO:9 in Claim 61. The claims recite embodiments for hybridomas, i.e., those producing antibody fragments, which are not described in the specification or known in the art.

The specification describes two hybridomas which produce full length antibodies each having a single idiotype as discussed under section 11, supra. The specification teaches numerous methods for producing hybridomas, purifying the secreted monoclonal antibodies and generating fragments from the monoclonal antibodies as well as recombinant technology for producing antibody fragments. The specification and

the art is silent with respect to a class of hybridomas which produce antibody fragments binding to the modified hepsin molecule of SEQ ID NO:9.

The claims encompass a genus of hyrbidomas defined solely by its principal biological property, which is simply a wish to know the identity of any material with that biological property. The claims encompass a class of hydridomas that were not in existence at the time of application filing or known in the field of art. Accordingly, there is insufficient written description encompassing a "hybridoma which produces the antibody fragment of Claim 48" (which binds the modified hepsin molecule of SEQ ID NO:9) because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a "the hybridoma" are not set forth in the specification as-filed, commensurate in scope with the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

In the absence of structural characteristics that are shared by members of the genus of a "hybridoma" which produces an antibody fragment that binds to a modified hepsin molecule of SEQ ID NO:9; one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

Thus, Applicant was not in possession of the claimed genus. See University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997).

Enablement

14. Claims 58-60 and 94-96 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir.1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention

Claims 58-60 are interpreted as being drawn to an immunoconjugate comprising an antibody that binds to the modified hepsin molecule of SEQ ID NO:9 joined to a therapeutic agent (Claim 58), and the agent is a cytotoxic agent (Claim 59) and the cytotoxic agent is ricin, doxorubicin, daunorubicin, paclitaxel (TAXOL™), ethiduim bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine,

dihydroxy anthracin dione, actinomycin D, diphteria toxin, Pseudomonas exotoxin (PE)A, PE40, abrin, glucocorticoid or a radioisotope (Claim 60). Claims 94-96 are drawn to an immunoconjugate comprising an antibody or antibody fragment produced by a hybridoma or the hybridomas designated ATCC PTA-4561 or ATCC PTA-5553 joined to a therapeutic agent (Claim 94), and the agent is a cytotoxic agent (Claim 95) and the cytotoxic agent is ricin, doxorubicin, daunorubicin, paclitaxel (TAXOL™), ethiduim bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin D, diphteria toxin, Pseudomonas exotoxin (PE)A, PE40, abrin, glucocorticoid or a radioisotope (Claim 96).

Because the implied use of the claims is for treating a disorder and more especially for killing a target cell with the cytotoxic agent, the claims are examined for enablement in therapeutic applications.

Disclosure in the Specification

The specification makes a general disclosure of using the antibodies to treat diseases such as cancer [0335] and for binding detecting, diagnosing, imaging and/or monitoring methodologies [0229; 0305; 0331] where hepsin protein is ordinarily expressed. The specification teaches detection methods such as immunostaining, FACs analysis and Western blotting (Examples 6-11). The specification does not provide a single example of one of the claimed immunoconjugates being used for treating (or preventing) any disease or disorder much less a cancer.

Status of Immunotherapeutics/Unpredictability/Undue Experimentation

In general, the use of antibody immunotherapy for the treatment of tumors has been shown to have limitations. Jain discloses the art known barriers to the delivery of drugs into solid tumors (Scientific American July 1994; cited in the PTO 892 form of 3/27/07). Impediments to drug delivery include (1) Nonuniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutics molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2).

Chatterjee et al state the art recognized experience that for any novel immunotherapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap (Cancer Immunol. Imunother., 1994, see Introduction; cited in the PTO 892 form of 3/27/07). Results obtained under controlled conditions and in

inbred animals, where nude mice are used as a test animal, often differ from the clinical response obtained in patients. This applies to strategies drawn to cancer therapy. For example, Dermer states that the widely disparate character of human tumor cells contributes greatly to chemotherapy's continued ineffectiveness against cancer (Biotechnology 12: 320, 1994; cited in the PTO 892 form of 3/27/07). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy in vivo. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

The specification does not disclose whether the immunoconjugates are effective in methods of treating a pre-existing disorder or tumor much less for inhibiting any hepsin-associated disorder, and this is a significant omission in view of the well-known immunosuppressive effects of certain tumors. The criticality of a working example encompassing the use of the immunoconjugates, especially the treatment of pre-existing neoplasia, is underscored by Gura et al (Science Vol 278 11/97 1041-1042; cited in the PTO 892 form of 3/27/07) in a discussion of potential shortcomings of extrapolating from in vitro studies and animal studies to similar procedures in cancer patients. Gura et al teaches that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, second col, second full paragraph) and that there were "gross difference in sensitivity in real tumors in mice and in the clonogenic assay" (page 1042, second col, second full paragraph). Further, Gura teaches that clonogenic assays "cannot tell researchers how anticancer drugs will act in the body"

(page 1042, first-second col, bridging paragraph). Thus, one skilled in the art would reasonably conclude that evidence obtained in the mouse xenograft models would necessarily correlate with results expected in human patients.

Although monoclonal antibodies have been shown to have specificity for the modified hepsin protein of SEQ ID NO:9, and monoclonal antibodies have been able to induce various degrees of tumor immunity for some diseases, not even a single example for a hepsin-associated disorder or disease much less a cancer appeared in the application (***i.e., intended use***) of the immunoconjugates as part of an immunotherapy. Therefore, it appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teachings of the specification and the prior art to treat any subject having just any disorder with the immunoconjugate of the instant claims.

As evidenced by Seaver (1994; Genetic Engineering Vol 14(14):pages 10 and 21; cited in the PTO 892 form of 3/27/07), selection of an antibody as an immunotherapeutic agent is an unpredictable task as the antibody must possess sufficient specificity and a high degree of affinity for its target for use as an immunotherapeutic agent and because these qualities are dependent on the physiology of the particular pathology and the accessibility of the target antigen. The specification is silent concerning what sort of specificity and affinity would be necessary for the hepsin antibodies of the claimed immunoconjugates so that one skilled in the art would not be able to practice the claimed invention without undue experimentation.

Therefore, due the unpredictability of immunotherapeutics in general, as evidenced by Jain, Chatterjee, Dermer, Gura and Seaver, and in view of the absence of any guidance and/or working examples concerning the use the hepsin antibodies as immunoconjugates, one skilled in the art would not know how to practice the broadly claimed invention, i.e., the implied use of the immunoconjugate for the treatment (or prevention) of any subject in need of thereof much less any hepsin-associated disease and its accompanying pathologies, including a cancer in any subject without undue experimentation.

Conclusion

14. Claims 62 and 63 are in condition for allowance.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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